corresponding populations. The calculated free energy values follow the same trend as the relative binding affinities of the nucleotides to the FtsZ protein.
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870-Pos Board B670
A new Boundary Element Formulation for Macromolecular Electrostatics
Randy Zauhar, LiFeng Tian.
We have implemented a new generation of the SMART molecular surface program, which features an improved approach for eliminating self-intersecting surface. The surface generator can produce a conventional polyhedral (flat triangle) approximation of the surface, or an accurate interpolation using cubic polynomials. This is coupled with a a new boundary element formulation for computing the molecular electrostatic potential under the continuum approximation. In contrast to our previous implementation, which required solution of a sparse system of simultaneous equations, the new approach minimizes an error functional, and is better-suited to current computing technologies (such as GPU-based calculation). Examples will be presented for model systems and protein-ligand complexes.

871-Pos Board B671
Vibrational Modes and Absorption Spectra of Large Biomolecules in the Harmonic Approximation
Saravana P. Thirumuruganandham, Adam J. Mott, Michael F. Thorpe, Peter Rez.
The analysis of low frequency vibrational modes can give insight into biologically significant motions in proteins and larger biomolecules such as protein complexes or viral capsids. In principle these can be calculated by finding the eigenvalues and eigenvectors of the all atom Hessian matrix, the second derivative of the potential energy with respect to atomic displacement. Due to the size of the all atom Hessian matrix, diagonalization becomes impractical for systems with 105-106 atoms. Various coarse graining schemes with a simplified description of the Hessian have been used, though there is a delicate balance between excessive coarse graining and increasing computational efficiency.
An alternative approach is to calculate vibrational densities of states and related electromagnetic absorption spectra from the Fourier transform of time correlation functions derived from Molecular Dynamics Trajectories. Since the forces are recalculated frequently, in many schemes at the end of every elementary time step, these simulations can be very time consuming especially if very low frequency modes are of interest. Rather than use molecular dynamics we solve the equations of motion for all the atoms in the harmonic approximation, a technique that has been used with great success in calculating the dynamical properties of amorphous semiconductors. The algorithm is fast and efficient since the same Hessian is used at all time steps. To demonstrate the validity of the approach we present calculated THz and infra red spectra for a number of small molecules in addition to proteins such as lysozyme and BPTI. The effects of anharmonic interactions are investigated by comparing our results with spectra calculated from molecular dynamics trajectories at different temperatures. Finally we show applications to large systems with up to a million atoms.

872-Pos Board B672
In Silico Modeling of Changes to Ventricular Myocyte Action Potential Morphology Caused by Pharmacological Agents
Kathleen R. McGovern, Amrita X. Sarkar, Eric A. Sobie.
Changes in electrocardiogram morphology associated with ventricular arrhythmias are one of the largest causes of the removal or restriction of marketed pharmacological agents and can be difficult to predict during drug development. Since changes to ECG morphology are the consequence of cellular-level alterations in the action potential, fresh insights can be gained by using computational models of cardiac action potentials and simulating drug-induced side effects. Although most pro-arrhythmic drugs block the rapid delayed rectifier current encoded by the gene commonly referred to as HERG, many drugs are non selective. With this in mind we analyzed mathematical models of ventricular action potentials to develop methods to predict non-specific, potentially pro-arrhythmic effects of new pharmacological agents. Through simulations, we generated predictions of changes in action potential duration (APD) caused by different concentrations of hypothetical drugs that specifically blocked with a defined affinity individual ion transport pathways (channels, pumps, or transporters). These relationships were empirically fit to the Hill equation. We then generated predictions of changes in APD caused by hypothetical drugs that blocked multiple pathways with different affinities. Based on linear transformations of the Hill equation fits and minimum least squares, our "reverse engineering" algorithm predicted the pathways that were most likely to be affected by a particular drug based on the APD versus [drug] relationship. Simulations were performed with the ten Tusscher model of the human ventricular myocyte in which hypothetical drugs blocked the rapid delayed rectifier current along with one of six other currents. When the results were fed to the algorithm in a blinded fashion, the program successfully identified the drug targets. The results show promise for the development of methods to determine potential channel candidates when the cause of APD disturbance is unknown.

873-Pos Board B673
Exploring RNA Drug Binding Using Consistent Charge Models
Joseph D. Yesselman, Hashim M. Al-Hashimi, Charles L. Brooks III.
RNA has emerged as a prospective drug target for a wide range of diseases. However, existing drug discovery tools optimized for protein targets have been largely unsuccessful in producing novel small molecules that target RNA due to RNAs distinct chemical and structural characteristics. Prevalent screening methods assay catalytic activity and are therefore unsuitable for RNA, as few RNAs are catalytically active. Furthermore, RNA has flexible binding sites, precluding the causal relationship between strong binding and inhibition of activity. Computational methods, including molecular docking, can overcome some of these limitations; however, RNA can adopt radically different conformations upon binding small molecules which can be difficult to model computationally. An additional challenge is that current force fields remain underdeveloped in modeling polyanionic nucleic acids with complex electrostatic interactions. Accurately capturing these interactions is crucial to determining precise free energy calculations of binding. We have developed a force field extension model that allows the same charges and force field parameters to be used for both the receptor and ligand, significantly improving the accuracy of capturing interactions between receptor RNAs and potential drug-like small molecules. Here we present details on our force field extension model, predicting the hydration free energy of 503 organic molecules using free energy perturbation demonstrating that our model reproduces experimentally confirmed results. Furthermore, we present docking results of predicted binding affinities and ligand-bound poses for a set of 60 known RNA-ligand complexes from the Protein Databank and compare results with other docking programs. Finally, we predict the binding affinities of 65 small molecules to the HIV-1 TAR RNA and compare results with a high throughput screen.

874-Pos Board B674
Modeling the Liposomal Rubidium Uptake Assay
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The liposomal radiotracer uptake assay is a useful technique in the study of the ensemble behavior of ion channels. For the study of potassium channels, purified channel protein is reconstituted into liposomes, in which an intra- to extra- liposomal K gradient is created. Uptake of radioactive 86Rb, added to the extra-liposomal solution, is concentrated into liposomes that have K selective channels, and is measured as a surrogate of channel activity. The assay allows one to define experimental conditions that are often difficult to control in other techniques used to study ion channels**,** such as membrane composition. The results of the assay are often interpreted qualitatively, but there are features of these results that remain poorly understood and a quantitative analysis is needed to make interpretations with greater confidence. We present here a quantitative analysis of this assay along with computational modeling. We examine the accumulation of $^{86}Rb^{+}$ into liposomes mediated by valinomycin and several purified K^{+} channels, and have developed a kinetic computational model based on the Goldman-Hodgkin-Katz flux equation assumptions. The model accurately reproduces uptake as a function of several experimental variables, including liposome number, radiotracer concentration, channel activity, and ionic concentration.

875-Pos Board B675
Singular Value Decomposition Technique for Model-Independent Analysis of Two-Component Datasets
Eric C. Landahl, **Sarah E. Rice**.
Singular value decomposition (SVD) algorithms are typically used to compress data or to solve for model-dependent parameters determined by a large dataset. SVD uses a small number of basis functions and a matrix giving the population of each basis function, whose sum best reproduces the data. One issue with SVD is that basis functions returned by these algorithms are not necessarily physically realistic, hence, SVD is mainly used for applications in which a randomly chosen basis will suffice. Here, we demonstrate that using a small number of realistic constraints, SVD can determine the basis functions that best represent large, two-component datasets in a model-independent way. The process is essentially to use an initial guess for a population model to obtain a basis, then apply known constraints to that basis and iteratively change the population model to meet those constraints. This new application is useful for deconvolving two-component spectroscopy data, in which the ''correct'' basis functions can be interpreted in terms of real physical states of the sample. We apply the